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Interrelationship of Neurogenic Obesity and Chronic Neuropathic Pain in Persons With Spinal Cord Injury

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The prevalence of obesity and of neuropathic pain are both estimated at above 50% in the population of people with chronic spinal cord injury (SCI). These secondary consequences of SCI have significant negative impact on physical functioning, activities of daily living, and quality of life. Investigations of relationships between weight or body composition and chronic neuropathic pain in people with SCI are lacking, but investigations in non-SCI cohorts suggest an association between obesity and the presence and severity of neuropathic pain conditions. In the present article, we present a review of the literature linking obesity and neuropathic pain and summarize findings suggesting that metabolic syndrome and chronic, systemic inflammation due to excess adiposity increase the risk for neuropathic pain after an SCI. **Key words:** *adipokines, chronic pain, inflammation, neuropathic pain, obesity, spinal cord injury*

Introduction

The co-occurrence of chronic pain and obesity, and correlations between chronic pain symptom severity and body mass index (BMI), have been repeatedly demonstrated.[1-6] This bi-directional relationship between nociceptive, or musculoskeletal, chronic pain conditions and body weight makes intuitive sense, given the impact that increased load can have on body structures, resulting in pain,[1] and the impact that chronic musculoskeletal pain can have in reducing exercise, thereby resulting in weight gain. The potential relationships between weight/BMI/adiposity and chronic neuropathic pain conditions is less obvious but has also been documented in the literature.[7] In the present article, we discuss the evidence for overlapping mechanisms related to neuropathic pain and obesity and suggest that neurogenic obesity should be studied as a potential risk factor for exacerbating neuropathic pain development and chronicity after traumatic spinal cord injury (SCI).

Neurogenic Obesity After SCI

Neurogenic obesity refers to the often co-occurring conditions of sarcopenic obesity due to muscle atrophy and osteoporosis, sympathetic blunting, anabolic deficiency, and blunted satiety[8,9] that occurs in more than 80% of individuals with SCI.[10] In addition to causing the clinical comorbidities associated with metabolic syndrome (i.e., dyslipidemia, hypertension, and type 2 diabetes mellitus), adipose tissue secretes a number of proinflammatory cytokines, including tumor necrosis factor α (TNFα), interleukin-1b (IL-1b), interleukin-6 (IL-6), monocyte chemoattractant protein-1 (MCP-1), and nuclear factor κB (NFκB).[10] Along with macrophages associated with adipose tissue, circulating monocyte and neutrophils are also increased, further enhancing the level of proinflammatory cytokines. These cytokines sensitize nociceptive neurons by increasing the expression and phosphorylation of voltage-gated

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Top Spinal Cord Inj Rehabil 2021;27(1):75-83

www.asia-spinalinjury.org
doi: 10.46292/sci20-00062

sodium (NaV) and transient receptor potential (TRP) channels.[11]

Given the complex reorganization that occurs at spinal and supra-spinal levels of the somatosensory nervous system after an SCI, coupled with the multiple consequences of neurogenic obesity, we propose that there is biologic plausibility for a reciprocal relationship between neuropathic pain and neurogenic obesity in SCI. We present existing literature in non-SCI populations to examine the pain-obesity association and the overlapping mechanisms that have been implicated in this association, and we apply it to the case of SCI.

Chronic Neuropathic Pain After SCI

Chronic pain is reported to be present in approximately 60% to 80% of the population with traumatic SCI,[12-14] with the majority of people reporting more than one chronic pain problem.[15] Clinical pain conditions are generally classified into two main types: *neuropathic* pain, which is due to "a lesion or disease of the somatosensory nervous system,"[16] and *nociceptive* pain, which does not involve nerve injury and is conducted via the intact somatosensory system.[16] Classification of nociceptive pains associated with SCI include musculoskeletal pains, visceral pains, and "other" nociceptive pains.[17] The most common type of nociceptive pain in persons with SCI is musculoskeletal pain, which often can be treated with physical therapy, reduced use, and a variety of nonaddictive pharmacologic agents.

The most recent international guidelines classify neuropathic pain in persons with SCI based on location relative to the neurological level of injury (NLI), as either at-level SCI pain (occurring within the area of the NLI and/or three dermatomes below the NLI), below-level SCI pain (occurring at least three levels below the NLI), or other neuropathic pain (may occur in any location but is not related to the SCI).[18,19] Pains that are neuropathic are typically considered more bothersome than nociceptive pains, due, in part, to the greater intensity of this type of pain, its nearly constant presence, and its persistent nature despite pharmacologic interventions.[15]

Despite its prevalence (occurring in approximately 50% of individuals with traumatic SCI[20]) and numerous studies focused on SCI-related neuropathic pain, there is still little consensus with regard to who is most at risk for chronic neuropathic pain. While some have reported a link between severity of injury (i.e., complete vs incomplete) or level of injury (i.e., cervical vs thoracic or lumbar) and the presence of neuropathic pain after SCI, most studies in the literature have indicated no significant differences in the prevalence of neuropathic pain related to these characteristics.[14,21-23] It is likely that a number of interrelated factors are needed to explain why approximately half of people with a traumatic SCI develop long-term neuropathic pain conditions. The present article considers the evidence that neurogenic obesity may be one of these contributing factors and is worthy of further study.

Relationship Between Obesity and Neuropathic Pain

The association between weight and chronic pain is well-established, with studies showing higher rates of pain complaints and of chronic pain diagnoses, as well as greater pain severity, for persons with higher BMI.[1,5,6] Higher body fat percentage and the presence of metabolic syndrome biomarkers have also been associated with clinical pain conditions.[2-4] With regard to relationships between chronic pain and weight specifically in persons with SCI, we found one study reporting higher ratings of pain severity (irrespective of type of pain) in persons with chronic SCI classified as either obese (defined as BMI > 30.0 kg/m^2 in that study), or underweight (BMI < 18.5 kg/m^2), when compared to persons with SCI in the normal weight (BMI between 18.5 and 24.9 kg/m^2) category.[24] Unfortunately, we could find no studies investigating the relationship between obesity and chronic pain in individuals with SCI with the newly accepted definition of obesity for SCI (i.e., BMI ≥ 22 kg/m^2)[25] or based on percent body fat criteria (>25% body fat for men, and 35% for women).[26]

Given the increased load that excess weight confers on the muscles, bones, and joints, it makes

sense that persons with higher BMI are more likely to suffer from nociceptive/musculoskeletal pain conditions, though other mechanisms contribute as well.[1] A recent systematic review demonstrated links between direct and indirect weight contributions, low physical activity, sleep disturbances, and adipose-related systemic inflammation on the reported perception of both chronic pain and stimulus-evoked pain.[6] A study of 3111 subjects with chronic pain from the Swedish Quality Registry for Pain Rehabilitation demonstrated reduced levels of physical activity in persons with both chronic pain and obesity, but it was unable to distinguish between pain or obesity as the primary etiology.[5] The relationship between obesity and chronic neuropathic pain, however, is not as well established, and the mechanisms by which obesity may be linked to *neuropathic* pain conditions are less obvious than those for musculoskeletal pain.

There are few published studies with the goal of examining a link between overweight/obesity status and prevalence of chronic neuropathic pain, although obesity has been reported as a risk factor for the development of postsurgical pain.[27] Postsurgical pain that persists beyond the healing time is labeled chronic postsurgical pain and is thought to involve mechanisms similar to those of other chronic central neuropathic pain conditions,[28] such as below-level SCI pain. With regard to the severity of pain, a small observational study found significant differences in pain severity between groups of overweight (BMI $\geq$ 25 kg/m^2; n = 14) and normal weight individuals (BMI < 25 kg/m^2; n = 30) with diagnosed neuropathic pain: The overweight group reported significantly higher overall pain scores (McGill Pain Questionnaire total score, p = .049) and higher neuropathic pain-specific symptom severity scores (Neuropathic Pain Symptom Inventory [NPSI] total score, p = .03) compared to the normal weight group.[7] These cross-sectional studies suggest that BMI and chronic neuropathic pain may be linked, but they provide little insight with regard to how or why. As approximately two-thirds of people with SCI are obese [8,29] and half have neuropathic pain,[30] research on the possible causal or shared mechanisms underlying the relationship between these conditions can have important quality-of-life implications.

Relationship Between Obesity and Signs of Somatosensory System Dysfunction Linked to Neuropathic Pain

Neuropathic pain is defined as pain caused by the presence of a lesion or disease of the somatosensory nervous system.[16] However, even in the absence of obvious neuropathic pain symptoms, signs of somatosensory dysfunction can be present that are precursors to the later development of neuropathic pain.[31-34] Thus, evidence of associations between obesity and measurable abnormalities of tactile, thermal, and pain sensitivity suggests a potential mechanistic link between obesity and somatosensory nervous system dysfunction that may lead to neuropathic pain. As this relationship has not been examined in people with SCI, evidence of the risk of neural impairment linked to obesity in non-SCI pain populations is reviewed below.

Abnormalities in pain sensitivity to evoked noxious stimulation can be accurately and reliably measured using quantitative sensory testing (QST) techniques.[35,36] Abnormalities in nociceptive thresholds or suprathreshold sensitivity obtained using QST in obese participants suggest neural dysfunction within the somatosensory system, either peripherally or centrally. Dodet et al.[37] reported that detection and pain thresholds to electrical stimulation delivered to the finger were higher for obese participants (n = 31) compared to normal-weight participants (n = 49), but that these thresholds did not change when the obese participants lost weight over a 6-month period (post gastric bypass surgery). These researchers interpreted their findings to mean that chronic obesity may establish persistent abnormalities in pain pathways that are difficult to "reset" to normal levels even after substantial weight loss.[37] However, the small sample size and a reported potential confound of age on pain threshold measures limits the impact of the results from this study. Other researchers, using thermal stimuli to measure warm and cool detection thresholds and hot pain thresholds, also reported higher thresholds for obese participants (n = 20) compared to age- and gender-matched nonobese controls (n = 20), when stimuli were presented on the abdomen.[38] However, they did not find differences for these thresholds when stimuli were delivered to the forehead. These

results showed only localized thermosensory impairment, suggesting peripheral, but not central, somatosensory dysfunction linked to excess adipose tissue in this relatively young (ages 18-45) and non-chronic pain cohort. Again, the small sample size in this study limits the impact and generalizability of these findings. Additional investigations will be needed to discern whether differences in somatosensory nerve function are reliably different between obese and nonobese individuals and the factors that influence differential sensitivity in these groups.

In persons with diagnosed neuropathic pain conditions, specific symptom profiles of self-report pain characteristics can be used to implicate and differentiate potential neuropathic pain mechanisms.[39] One study used the subscale scores of the NPSI[40] for comparison between normal- and high-BMI (defined as >25 kg/m^2) subgroups of study participants with neuropathic pain.[7] They reported significantly higher scores for the high-BMI group on the "paresthesia/dysesthesia" and "paroxysmal" subscales of the NPSI, but no differences between BMI groups on other subscales of the NPSI (superficial spontaneous/"burning" pain, evoked pain, and deep spontaneous pain). The specific symptom of high paresthesia/dysesthesia (i.e., "numbness") was suggested by the authors to indicate greater loss of nerve function in obese, compared to normal-weight, individuals with neuropathic pain.[7]

Potential Mechanisms Linking Neuropathic Pain and Obesity

Mechanisms that have been posited to explain the relationship between obesity and neuropathic pain include metabolic syndrome, inflammation, and dysregulation of certain neurotransmitters (i.e., dopamine and serotonin), each of which is more common in people with SCI than in the general population.[8,41,42]

Metabolic syndrome

Obesity is tightly linked to metabolic syndrome, which includes a combination of symptoms such as impaired glucose tolerance, impaired fasting glucose, hypertension, dyslipidemia, and/or microalbuminuria.[10] Some of these components of metabolic syndrome have been linked to nerve dysfunction and resultant neuropathic pain.[43-45] Impaired glucose tolerance is associated both with peripheral neuropathy,[43] evidenced by measures of impaired nerve action potentials[46,47] and large and small fiber sensory impairment,[47] and with increased incidence of neuropathic pain symptoms.[48-50] Intermittent and chronic hyperglycemia have also been linked to changes in sensory nerve responsiveness, conduction velocity, and increased behavioral response (i.e., pain) to noxious stimulation.[43,51] Many of the relationships between metabolic syndrome markers and neuropathy and neuropathic pain were found not only in those diagnosed with diabetes but also in those who did not meet clinical criteria for diabetes.[43]

Inflammation

Several studies, in a variety of patient populations, have shown that obese individuals have higher levels of inflammatory markers, including IL-6, TNFα, and C-reactive protein, when compared to nonobese individuals.[52,53] Secretion of proinflammatory cytokines occurs in the adipose tissue, with monocyte chemoattractant protein 1 (MCP-1) attracting monocytes to adipose tissue and stimulating the monocytes to release inflammatory cytokines.[52] This continued process of adipokine secretion contributes to the maintenance of the systemic heightened inflammatory state in obesity. Adipose-secreted cytokines sensitize nociceptive neurons by increasing the expression and phosphorylation of NaV and TRP; it remains unclear what role these systemic cytokines may have on the central nervous system mediators of pain transmission.[11]

For people with SCI, sarcopenia is initiated almost immediately after injury.[54] This increase in the ratio of adipose tissue to muscle mass conveys an obesity status, even if weight/BMI does not change. This disproportionate increase in adiposity after injury can chronically sustain the systemic inflammatory state, even in the presence of "normal" weight or BMI (based on standard/non-SCI cutoffs), which can impact a number of secondary conditions,[10] possibly including neuropathic pain,

although there is currently no literature that directly supports the relationship between adiposity-related inflammation and neuropathic pain in SCI.

The chronic and systemic presence of pro-inflammatory mediators can lead to impaired somatosensory nervous system function, which sets the stage for the development and maintenance of neuropathic pain conditions. Sustained levels of inflammation in response to the presence of disproportionate adipose tissue include increased production of prostaglandins, bradykinin, and histamines, which are known to interact with sensory nerves to alter responsiveness within the nociceptive system.[55,56] Interrelationships between obesity, levels of leptin (an adipokine), and evoked pain thresholds,[37,57-59] as well as increased report of persistent pain conditions,[60] are documented in the literature.

Given the demonstrated effect of adipose tissue on proinflammatory mediators, and the impact that inflammation can have on nerve function, it can be hypothesized that preexisting adiposity and/or postinjury increases in adiposity may increase the risk for developing neuropathic pain after injury to the spinal cord. The cascade of mechanisms that is initiated by the SCI itself includes prolonged inflammatory responses that can be further enhanced if systemic adipokines are also present to reinforce hyperresponsivity within the nociceptive system. The presence of additional inflammatory mediators in the setting of a traumatic SCI has implications for at-level neuropathic pain, and, when adipokines persist or increase over time, may also contribute to supra-spinal mechanisms involved in refractory below-level neuropathic pain. A recent randomized, parallel group, controlled clinical trial supports this hypothesis, demonstrating the efficacy of a 12-week anti-inflammatory diet intervention (vs usual diet) in significantly reducing both systemic inflammatory biomarkers and neuropathic pain symptom severity in individuals with chronic (≥ 2 years) SCI.[61] However, this investigation was based on a small cohort, with 12 individuals in the anti-inflammatory diet condition and 8 in the control diet condition, and did not report any measures of weight or body composition/adiposity. Thus, the direct influence of adipose tissue-induced inflammation on neuropathic pain cannot be made.

Reciprocal Associations and Overlapping Mechanisms of Obesity, Depression, Sleep Disorders, and Chronic Pain

Depression has been found to frequently co-occur with obesity and with chronic pain in the general population.[5,52,62] Similarly, poor sleep quality is a common complaint in overweight/obesity and chronic pain populations.[1,5,63] Evidence from the literature suggests that these relationships may be even more pronounced in persons with SCIs. One study, in a large group of individuals with physical disabilities (muscular dystrophy [n = 339], multiple sclerosis [n = 579], post-polio syndrome [n = 443], and SCI [n = 488]), found that study participants classified as having an obese BMI (≥30 kg/m^2) and/or high-risk abdominal obesity (BMI ≥25 kg/m^2 and waist circumference > 40 inches for males or > 35 inches for females) had significantly higher pain interference, sleep disturbance, and sleep-related impairment compared to persons classified as nonobese.[64] Another study investigated the link between depression, anxiety, and obesity in persons with SCI and compared the presence and associations between these conditions to persons without SCI.[65] Their findings showed that not only do individuals with SCI have three to four times the odds of diagnosis for anxiety disorders, depressive disorders, and overweight/obesity than non-SCI individuals, but also that, within the SCI group, being diagnosed as overweight/obese conferred even higher odds of having concomitant depression and anxiety compared to persons with SCI who did not have an overweight/obese diagnosis. In addition, prevalence of sleep-disordered breathing, which is often associated with obesity, is also much higher in the SCI population than in nondisabled populations.[66,67] Thus, pain severity, depressive symptomatology, poor sleep, and obesity status often vary together, suggesting reciprocal relationships between overlapping mechanisms.

Among the potential mechanisms related to the inter-associations between obesity, pain, and other poor outcomes in the SCI population are inflammatory mediators and certain neurotransmitters, such as serotonin. Dysregulation in levels of serotonin has been associated with chronic pain, which may indicate that serotonin plays a role as a predisposing condition for the

development of chronic pain, or that serotonin dysregulation is a result of having a chronic pain condition.[68] Serotonin is also known to play an important role in regulating sleep cycles, mental health, and obesity.[69,70] Increased levels of the adipocyte indoleamine 2,3-dioxygenase (IDO) can lead to reductions in the production of serotonin by tryptophan, and reduced levels of serotonin are tied to both depressive symptoms[71,72] and to somatosensory abnormalities and neuropathic pain.[73] Additionally, the use of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), developed for use in those with depression, is one of the few effective treatments for some central neuropathic pains,[74] such as below-level pain in SCI.[75]

As described earlier, peripheral and central nociceptive system mechanisms are impacted by the systemic inflammation produced by excess adiposity in obesity. Additionally, inadequacies in the amount and quality of sleep, which are common in persons with SCI and obesity, also promote production of proinflammatory cytokines. It has been shown that hypoxemia due to obstructive sleep apnea results not only in increases in inflammatory mediators but also in corresponding increases in sensitivity to evoked pain and self-report ratings of clinical pain severity.[76,77]

Summary

A traumatic injury to the spinal cord causes an immediate cascade of inflammatory responses that, among other things, can initiate hypersensitivity within nociceptive pathways leading to chronic neuropathic pain in 50% of those injured. The presence of metabolic syndrome and ongoing, systemic inflammation conferred by neurogenic obesity after an SCI may also contribute to the initiation or exacerbation of neuropathic pain symptoms. Although there is a paucity of literature demonstrating a causal link between obesity and neuropathic pain in SCI, it would appear that this would be a fruitful, if not essential, line of investigation and one in which a majority of persons with chronic SCI would benefit. Establishment of an internationally accepted classification of pain after SCI (via the International SCI Pain Classification and the International SCI Pain Basic Dataset[17,19]) and appropriate cutoffs for defining obesity in SCI (BMI ≥22 kg/m^2)[25] have set the stage for undertaking such studies. However, longitudinal studies that are needed to evaluate the direction and strength of relationships, and to uncover the mechanisms responsible for these relationships, will likely require large subject numbers to account for subject attrition and heterogeneity, expensive equipment, and time-consuming assessments. In addition, measuring specific components of neurogenic obesity, including assessing body composition metrics, and differentiating neuropathic pain phenotypes will be important for clarifying mechanisms and guiding targeted interventions to prevent these negative consequences of SCI.

Conflicts of Interest

The authors declare no conflicts of interest.

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